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This Month in *AJP*

Defining Age-Dependent Biomarkers in the CSF Proteome

To achieve success with diagnostic assays of cerebrospinal fluid (CSF) biomarkers in age-related neurodegenerative diseases, the nature of the CSF proteome in normal aging must be understood. Baird et al (Am J Pathol 2012, 180:446–456) used a novel proteomic technology (SOMAmer) to quantify hundreds of CSF proteins from 90 cognitively normal adults (aged 21 to 85 years). They detected 248 proteins with signals greater than twofold over background. Several novel correlations indicated that both inflammation and response to injury in the central nervous system may increase with age. Such a biomarker profile, if validated, could thus be useful in studies of normal and pathological central nervous system aging.

Inducing Gut Barrier Maturation with Probiotic Bacteria

Impaired intestinal barrier function has been implicated in the pathogenesis of infectious enteritis, inflammatory bowel disease, and necrotizing enterocolitis. Patel et al (Am J Pathol 2012, 180:626–635) report that commensal bacterial colonization induces intestinal barrier function maturation by promoting claudin 3 expression, a key component of tight junctions. Neonatal mice raised on antibiotics or those lacking MyD88 exhibited impaired barrier function and decreased claudin 3 expression. Enteral administration of either live or heat-killed preparations of the probiotic *Lactobacillus rhamnosus GG* accelerated intestinal barrier maturation and induced claudin 3 expression while live *L. rhamnosus GG* increased mortality. These data indicate that probiotic administration can accelerate the maturation of both claudin 3 protein expression and intestinal barrier function in an immature gut lacking commensal bacteria, possibly preventing intestinal inflammatory diseases.

A Novel Murine Model of Myasthenia Gravis

Myasthenia gravis (MG) is caused by autoantibodies against postsynaptic membranes at neuromuscular junctions (NMJs). However, antibodies against muscle-specific kinase (MuSK) do not act via the complement pathway. To investigate the pathophysiology of MuSK-MG, Mori et al (Am J Pathol 2012, 180:798–810) injected MuSK protein into mice deficient in complement protein C5. MuSK-injected mice developed severe muscle weakness, with an electromyographic pattern similar to that observed in MG patients. Morphological and functional defects in NMJs confirmed that complement activation is not necessary for MuSK-MG onset. Furthermore, MuSK-injected mice exhibited a loss of acetylcholine receptor expression, as well as reduced size of motor terminals apposing acetylcholine receptor clusters at NMJs. Thus, disruption of MuSK activity by autoantibodies triggers MG. This experimental MG model could be useful in developing appropriate medications for the treatment of MuSK-MG in humans.

Can Cells Express Both Hematopoietic and Mesenchymal Markers in Normal Bone Marrow?

Bone marrow (BM) fibrosis is a feature of severe hyperparathyroidism, and mice overexpressing constitutively active parathyroid hormone (PTH)/PTH-related peptide receptors in osteoblasts (PPR∗Tg) exhibit BM fibrosis. To gain insights into the complexity of the BM stroma, Ohishi et al (Am J Pathol 2012, 180:811–818) generated a double-mutant mouse that also expresses GFP under the control of the type I collagen promoter (PPR∗Tg/GFP). A GFP^+CD45^+ cell population was identified in the BM of both PPR∗Tg/GFP and control animals, though it was expanded in PPR∗Tg/GFP mice. The existence of cells expressing both type I collagen (ie, GFP^+) and CD45 in the adult BM was confirmed by IHC and FACS. mRNA expression of type I collagen and PTH/PTH-related peptide receptor and receptor activator for NF-κB was confirmed, further supporting features of both mesenchymal and hematopoietic lineages. These findings indicate that the BM is a permissive microenvironment for the differentiation of fibrocyte-like cells and raise the possibility that these cells could contribute to the pathogenesis of BM fibrosis.

FOXA1 and Castrate-Resistant Prostate Cancer

Forkhead box protein A1 (FOXA1) modulates the transactivation of steroid hormone receptors and thus may influence tumor growth and hormone responsiveness in prostate cancer. Gerhardt et al (Am J Pathol 2012, 180:848–861) investigated the correlation of FOXA1 expression with various disease parameters in a large cohort of prostate cancer patients at different disease stages. FOXA1 expression increased from primary prostate carcinomas of the peripheral zone and metastases to castration-resistant prostate cancer, reflected by a correlation with higher Gleason scores, higher tumor stages, and faster biochemical disease progression (the last particularly in cases with lower androgen receptor levels). siRNA knockdown of FOXA1 induced decreased cell proliferation and migration, and full *in vitro* tumorigenicity of the androgen-dependent prostate cancer cell line LNCaP required FOXA1 expression. Thus, FOXA1 represents a novel mechanism of castration resistance and a novel candidate therapeutic target.